Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 15-23 were rejected as failing to define the invention in the manner required by 35 U.S.C. § 112, second paragraph. The Examiner states that the form of the claims are improper. Claims 15-23 have now been canceled and rewritten to alleviate this ground of rejection.

Claims 5 and 14-23 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claim 5 has now been canceled, thus rendering this ground of rejection moot.

Claims 14-23 have been canceled and rewritten such that it is believed that this ground of rejection has been alleviated.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1-8, 15-21, and 23 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the claims do not disclose strains of bacteria which fulfill the requirement of releasing low molecular weight proteins under certain conditions of stress. Applicant wishes to point out to the Examiner that the exact characterization of these SRF's has not been determined and as described in the specification they may include nucleotides, peptides, lipids and carbohydrates. As discussed in the § 132 Declaration herewith, SRF's have an absorption maximum at 254nm indicating nucleotides, not

proteins. In any event, the claims have now been limited to set forth the classes and species of bacteria which have been shown to produce stress factors. Thus, Applicant respectfully requests that this ground of rejection be withdrawn.

Also, claims 1-7, 16-21, and 23 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification is not enabling for claims directed to modulation of the immune system. It is well established that a patentee may be his own lexicographer with respect to terms used in the specification. Page 9, first paragraph of the specification states that the phrase "modulating an immune response in animals" is defined as (a) stimulating an immune response by activating macrophages to release immune stimulating interleukins IL-1, IL-6 and TNF; (b) down-regulating the CD-14 receptor of macrophages to prevent overstimulation by endotoxin leading to the over-production of IL-1, IL-6 and TNF, associated with systemic inflammation, cardiovascular dysfunction, shock and death; and (c) down-regulating the CD-16 receptor or macrophages to prevent overstimulation by IL-10 leading to the overconversion of macrophages to their cytotoxic phenotype with its potential for excessive destruction of host cells. Further, a publication appeared this fall (Heidenreich et al, J. Immunol., 1997, 159:3178) copy attached, stating that the CD14 receptor on the surfaces of macrophages can trigger survival of the macrophage or its suicide, ("apoptosis" or "programmed

cell death"). Their "default" setting is to die within a day or so after being formed in the bone marrow and released into the blood, unless activated. Lower levels trigger them to die. Paradoxically, the host will not survive if activation of the macrophage is excessive, induces the release of excessive amounts of interleukins, which can lead to fever, a low heart rate, and organ shutdown. Therefore, the SRFs can truly modulate the immune system leading to an appropriate response. It is submitted that the specification is sufficiently enabled for these purposes.

Claim Rejections - 35 U.S.C. § 103

Claims 1-5,6,7,15, and 23 were rejected under 35 U.S.C. § 103 as being unpatentable over De Vuyst.

The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). It is axiomatic that in order to establish a prima facie case of obviousness, it is necessary for the examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. See e.g. Carella v. Starlight Archery, 804 F.2d 135 (Fed. Cir. 1986); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985). This suggestion cannot stem

from the applicant's own disclosure, however. In re Ehrreich, 590 F.2d 902 (CCPA 1979).

The same inquiry must be carried out in the context of a proported obvious "modification" of the prior art. In re Fitch, 23 U.S.P.Q.2d 1780, 1783-84 (Fed. Cir. 1992). Thus, the initial burden of proof is on the Examiner. In re Warner, 379 F.2d 1011, 1016 (C.C.P.A. 1967). Only after the Examiner establishes a prima facie case of obviousness does the burden shift to the applicant to provide evidence of nonobviousness. Levengood, 28 U.S.P.Q.2d at 1301, n.1.

De Vuyst teaches the production of a bacteriocin produced by *Lactobacillus amylovorus* DCE 471 which is bacteriocidal towards closely related *Lactobacillus* strains. (p. 818). De Vuyst further discloses that the bacteriocin-producing lactic acid bacteria could potentially be added to foods to stimulate bacteriocin production. (p. 825).

It is submitted that the Examiner is misinterpreting applicants invention which is not related to bacteriocins. Submitted herewith is a § 132 Declaration of Dr. Marshall which clearly establishes that he SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties. The declaration details several experiments conducted using the methods of the invention and exposing the SRF compositions to *Lactobacillus helveticus*. The results show that the SRF compositions do not exhibit bactericidal activity. The results as depicted in Photograph

1 demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum*, and *E. faecium* DO NOT inhibit growth of Lactobacillus helveticus. This is in stark contrast to the bacteriocin Nisin which is shown at the asterisk. Figure 2 shows that stressing *L. monocytogenes*, or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bacteriocidal activity against *L. helveticus*. Figure 3 demonstrates that bacteriocins against *L. helveticus* are not produced by stressing *L. caseii*, *L. plantarum* or *E. faecium*, again no zones of inhibition are observed from the SRF's. Finally in Figure 4, 7 test strains (5 of *L. plantarum* and 2 of *E. faecium*) were used both as SRF collecting strains and as test strains. Again, the bacteriocin Nisin inhibited all 7 strains while the SRF's collected from the same strains as well as from *L. caseii* did not inhibit growth.

In contrast to the bacteriocin described in De Vuyst, the present invention claims the activation or modulation of the immune system of an animal through the administration of a product produced by bacteria subjected to stress which is then filtered. De Vuyst does not disclose the administration of a bacterial product to an animal which has been filtered from the bacteria, and it further does not teach that the product has been filtered to remove any molecules larger than 10 kDa.

Further, new claim 24 sets forth that the SRF's are administered to the animal in one of several specified

delivery forms, including gels for oral delivery and nasal sprays, as described in claim 18, now canceled. Since De Vuyst does not suggest the use of these delivery systems, new claims 24-35 are also not rendered obvious by De Vuyst.

In addition, new claim 34 sets forth the specific species of bacteria from which Applicant's product can be derived, none of which include *Lactobacillus amylororus* strain, as described in De Vuyst. Since *Lactobacillus amylorus* strain is the only strain of bacteria which produces the amylovorin L471 bacteriocin described in De Vuyst, claim 35 i4 also not rendered obvious by De Vuyst.

Claims 16, 18, and 19 were rejected as being obvious by De Vuyst in view of Nanji. These claims were canceled and their substance incorporated into new claims 24-34.

As set forth above, De Vuyst does not teach the administration of a nonbacteriocidal product which is collected and filtered to remove molecules larger than 10 kDa, as required by new claim 24. Nanji also does not provide this missing teaching. Instead, like De Vuyst, Nanji teaches the administration of the *Lactobacillus* bacteria itself. In addition as described in the 132 declaration herewith, Nanji teaches a unique Lactobacillus that can be fed to animals to reduce blood endotoxin levels. Nanji assumes that reduced levels of blood endotoxin reflect the destruction of Gram-negative organisms in the gut by overgrowth of the lactobacillus. There is no teaching or recognition in Nanji

that a protective effect may be achieved without administration of the lactobacillus itself by harvesting the factors produced by the bacteria and administration of them instead of the bacteria. In fact, Nanji teaches away from the invention by asserting that colonization of Lactobacillus growth after administration is required for any effect. Thus, the claims are not rendered obvious by De Vuyst in view of Nanji.

Claim 20 was rejected as being obvious over Perdigon. Claim 20 was also rejected as being obvious over Farr. Claim 20 has now been canceled, thus rendering each ground of rejection moot.

Claim 21 was rejected as being obvious over De Vuyst in view of Perdigon. Claim 21 has been canceled, thus rendering this ground of rejection moot.

Applicant however would like the following comments about Perdigon and Farr made of record. Perdigon discloses a teaching of a protective effect of lactobacilli due to an interaction between milk solids and the bacteria. She states that the immune-enhancing effect of the lactobacilli was due to products created by lactobacilli fermenting milk proteins and the action of milk derived lysozyme on bacteria already established in the gut. There is absolutely no teaching that any desired effect can be achieved by administering factors collected from the stressed bacteria and without milk solids.

Farr discloses a unique strain of *L. lactis* which is able to restrict the growth of other organisms after ingestion. As seen earlier, applicants factors do not themselves contain any bactericidal activity. Also again, applicants invention does not involve the feeding of bacteria directly to an animal but of small molecular weight products harvested from the supernatant of stressed bacteria. As discussed earlier *L. caseii*, *L. fermentum*, *L. acidophilous* and *Listeria monocytogenes* did not inhibit the growth of *E. Coli* in lab media.

Claim 21 was also rejected as being obvious over De Vuyst in view of Emery. This ground of rejection is rendered moot. Briefly, however applicant would like to comment on Emery. Emery teaches the use of a subcutaneous implant to release an immunogen and induce the formation of specific antibodies. The immunogens disclosed are as large as 30kDa. The SRP's referred to in the patents are Siderophore-Receptor-Proteins not Stress Release Products. There is no teaching of harvesting a Stress Response product that may not even be proteins and administering it to an animal.

For the above-stated reasons, it is submitted that the present invention is in a prima facie condition for allowability. Allowance is respectfully requested.

It is not believed that any fees are due with this response. If a fee is required, please consider this a request to debit Deposit Account 26-0084 accordingly.

Respectfully submitted,

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